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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,722	07/10/2006	Rosanne M Crooke	BIOL0004USA	6604
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Isis Pharmaceuticals, Inc.				
222 East 41st Street				
New York, NY 10017-6702				
EXAMINER				
GIBBS, TERRA C				
ART UNIT		PAPER NUMBER		
1635				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

<b>Application No.</b> 10/553,722	<b>Applicant(s)</b> CROOKE ET AL.
<b>Examiner</b> TERRA C. GIBBS	<b>Art Unit</b> 1635

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 14 November 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
 Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☒ The Notice of Appeal was filed on 14 November 2008. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☒ Applicant's reply has overcome the following rejection(s): Claims 61, 65-70, and 72-76 will not be provisionally rejected under the judicially created doctrine of double patenting over claims 23, 38, 39, 45-62 and 64 of copending Application No. US Publication No. 2004/0208856 ('856). This rejection is withdrawn because the claims of '856 are drawn specifically to methods of treating hyperlipidemia, delaying the onset of hyperlipidemia, lowering cholesterol, and lowering serum and plasma triglyceride levels in an animal, while the methods of the instant invention are drawn specifically to methods of ameliorating hepatic steatosis and lowering liver triglyceride levels in an animal.

6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 61, 65-70, 72-76 and 84-99

Claim(s) withdrawn from consideration: \_\_\_\_\_

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_
13. ☐ Other: \_\_\_\_\_

/Sean R McGarry/  
Primary Examiner, Art Unit 1635

U.S. Patent and Trademark Office  
PTOL-303 (Rev. 08-06)

**Advisory Action Before the Filing of an Appeal Brief**

Part of Paper No. 20081215

Continuation of 11, does NOT place the application in condition for allowance because: Claims 61, 65-70, 72-76, and 84-99 will remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shachter, N. (Applicant's Reference BF on the Information Disclosure Statement filed August 14, 2007), in view of GenBank Accession No. NT\_035088 (Applicant's Reference BL on the Information Disclosure Statement filed August 14, 2007), Jong et al. (Arterioscler Thromb Vasc Biol., 1999 Vol. 19:472-484), Senior, K. (Drug Discovery Today, 2002 vol. 7:840-841, Applicant's Reference BE on the Information Disclosure Statement filed August 14, 2007), and Monia et al. (Applicant's Reference AE on the Information Disclosure Statement filed August 14, 2007). In response to this rejection, Applicants argue that none of the cited references, whether considered alone or in combination, teach or suggest that antisense inhibition of apolipoprotein C-III might result in amelioration of hepatic steatosis or reduction in liver triglyceride levels in an animal. This argument has been fully considered, but is not found persuasive because Shachter et al. teach, "Increased expression of apoC-III may be the mechanism of the hypertriglyceridemic phenotype" [in liver biopsies] (see page 298, second column, first paragraph). Further, Shachter et al. teach that decreasing apoC-III gene expression has a triglyceride-lowering effect (see paragraph bridging pages 298 and 299). Based on these disclosures, one skilled in the art would envision that decreasing apoC-III gene expression would have a triglyceride-lowering effect in the liver specifically because Shachter et al. also teach that apolipoprotein C-III has been shown to directly interfere with triglyceride-rich emulsions and lipoprotein clearance in the liver (see page 297, second column, second paragraph). Thus, it is the Examiner's position that, based on the explicit teachings of Shachter et al., one skilled in the art would believe that the reduction of apolipoprotein C-III would lead to a decrease in hepatic uptake of triglycerides.

Applicants also argue that none of the cited references, either alone, or in combination provide a reasonable expectation that Applicant's claimed methods would succeed. This argument has been fully considered, but is not found persuasive because Senior was relied upon primarily to teach an expectation of success in administering to an animal, an antisense compound that specifically hybridizes with a nucleic acid molecule encoding a lipoprotein. While it is true that Senior does not mention antisense compounds that are 100% complementary to ApoC-III specifically, it is the Examiner's position that an artisan of ordinary skill could take the successful teachings of Senior and apply them with a reasonable expectation of success in combination with Jong and Shachter, N. and GenBank Accession No. NT\_035088 to arrive at Applicant's invention. Furthermore, Senior explicitly discloses, "[D]eveloping antisense drugs depends very much on identifying an appropriate target" (see page 840, first column). It is noted that this criteria has been fully met and satisfied since GenBank Accession No. NT\_035088 teaches a nucleotide sequence that codes for human apolipoprotein C-III. Senior also explicitly discloses, "[A]ntisense technology, by contrast, is a successful approach [emphasis added] because the oligonucleotides that match the sequence of the gene stop translation of the mRNA in the liver" [emphasis added] (see page 840, second and third columns). Thus, given the teachings of Senior, the artisan of ordinary skill could easily take the identified target provided by GenBank Accession No. NT\_035088, design antisense that match the sequence of the gene to subsequently stop translation of the mRNA in the liver, which would in turn lead to the identification and selection of therapeutic antisense agents 100% complementary to SEQ ID NO:4 for use in treating the disorders recited in Applicant's claims. Therefore, the combined teachings of Senior, K. and GenBank Accession No. NT\_035088 provide one of ordinary skill in the art with a reasonable expectation of success to practice the methods as claimed.

Applicants next argue that the cited art teaches away from the claimed invention. For example, Applicants contend that Shachter indicates that apolipoprotein C-III has been shown "to directly interfere with their [triglyceride-rich emulsions and lipoprotein] hepatic clearance" (see page 297, second column, second paragraph). Applicants contend that based on this teaching, one of the functions of expressed apolipoprotein C-III protein is to reduce uptake of triglycerides by the liver. Applicants argue that Jong et al. also support Applicant's argument that the cited art teaches away from the claimed invention. Accordingly, Applicants argue that one skilled in the art might expect that reduction of apolipoprotein C-III would lead to increased hepatic uptake of triglycerides and ultimately lead to increased triglyceride accumulation in the liver. It should be noted that although this argument was never presented while prosecution was open in the instant case, the Examiner will address this new argument, but briefly. This new argument has been fully considered, but is not found persuasive because in no way does the cited art teach away from the claimed invention. This is primarily because Shachter et al. teach, "Increased expression of apoC-III may be the mechanism of the hypertriglyceridemic phenotype" [in liver biopsies] (see page 298, second column, first paragraph). Further, Shachter et al. also teach that decreasing apoC-III gene expression has a triglyceride-lowering effect (see paragraph bridging pages 298 and 299). Based on these disclosures, one skilled in the art would envision that decreasing apoC-III gene expression would have a triglyceride-lowering effect in the liver specifically because Shachter et al. also teach that apolipoprotein C-III has been shown to directly interfere with triglyceride-rich emulsions and lipoprotein clearance in the liver (see page 297, second column, second paragraph). Therefore, it is the Examiner's position that, based on the explicit teachings of Shachter et al., one skilled in the art would believe that the reduction of apolipoprotein C-III would lead to a decrease in hepatic uptake of triglycerides and lead to a decrease in triglyceride accumulation in the liver and hepatic steatosis.